OUTCOMES OF COMBINED MODALITY THERAPY FOR BREAST CANCER WITH ISOLATED IPSILATERAL SUPRACLAVICULAR NODAL METASTASES AT PRESENTATION

This dissertation is submitted to

THE TAMILNADU

Dr. MGR MEDICAL UNIVERSITY

in partial fulfillment of the requirements for the award of degree of

MCh (BRANCH VII)

SURGICAL ONCOLOGY

COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI – 600 020

AUGUST 2011

CERTIFICATE

I hereby certify that this dissertation on ***"Outcomes of combined Modality Therapy for Breast cancer with Isolated ipsilateral supraclavicular nodal metastases at presentation"*** is a bonafide work done by **DR.V.VENKTESH,** in the department of Surgical Oncology,College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance and supervision, to my satisfaction.

Prof. E.HEMANTH RAJ MS, M Ch, PhD
Additional Director and Chairman
Division of Surgical Oncology
Cancer Institute (WIA)
Adyar, Chennai – 36.

ACKNOWLEDGEMENT

I express my sincere thanks and deepest sense of gratitude to our Professor and Chairman, Division of Surgical Oncology, Dr E Hemanth Raj M Ch PhD, for his scholarly guidance, masterly supervision, and encouragement in completing this project.

I humbly record my deep sense of gratitude to **Dr. Sridevi** M Ch, Professor, Division of surgical oncology, for her constant support, encouragement and guidance during the course of this study.

Words are few to express the gratitude and the inspiration I have drawn from the leaders in the realm of oncology in India, **Dr. Krishnamurthy**, Advisor and **Dr. V Shantha**, Executive Chairman, Cancer Institute(WIA).

The task would have been indeed more difficult without the help of the staff of Tumor Registry at Cancer Institute (WIA), who had the unenviable task of procuring all the case records instantaneously on demand.

Last but not the least, I thank all my patients for their kind co-operation in this study.

CONTENTS

AIMS OF THE STUDY

1. To determine the incidence of isolated ipsilateral supraclavicular nodal metastases at presentation, in patients with carcinoma breast.

2. To study the outcomes in response rates, disease free survival, overall survival in patients with carcinoma breast who presented with ipsilateral supraclavicular nodal metastases.

3. To determine the factors affecting the disease free survival (DFS) and overall survival (OS).

BACKGROUND

The female breast has been an organ of fascination and so also the treatment of breast cancer. The treatment of breast cancer has remained an enigma from the ancient past to present day .Tremendous progress has been made in the management of carcinoma breast. Despite this, the treatment is still a complex issue. Breast cancer is a major public health problem for women throughout the world. In India, breast cancer remains the most common cancer in urban women.

Since 1990, the death rate from breast cancer has decreased in the United States by 24% and similar reductions have been observed in other developed countries.[1,2] Mathematical models suggest that both the adoption of screening mammography and the availability of adjuvant chemotherapy and tamoxifen have contributed approximately equally to this improvement.[3] Although breast cancer has traditionally been less common in non industrialized nations, its incidence in these areas is increasing. Multiple factors are

associated with an increased risk of developing breast cancer, including increasing age, family history, exposure to female reproductive hormones (both endogenous and exogenous), dietary factors, benign breast disease, and environmental factors.

Invasive breast cancers constitute a heterogeneous group of lesions that differ with regard to their clinical presentation, radiographic characteristics, pathologic features, and biologic behavior. The most common histologic type of invasive breast cancer is invasive (infiltrating) ductal carcinoma. The most widely used histologic grading is that proposed by Elston and Ellis and is a modification of the grading system proposed by Bloom and Richardson. It is based on tubule formation, nuclear pleomorphism, and mitotic activity.[4] Patients are staged according to The American Joint Committee on Cancer (AJCC) TNM staging system, 2009.

The patients are broadly divided into three groups for the purpose of management. Early breast cancer (EBC), Locally advanced breast cancer (LABC) and Metastatic breast cancer (MBC). Though the incidence of early breast cancer is rising in

the developed countries, in India many patients still present with locally advanced breast cancer.

Patients with LABC include those with

1. operable disease at presentation (clinical stage T3N1),
2. inoperable disease at presentation (clinical stage T4 and/or N2-N3)
3. inflammatory breast cancer (clinical stage T4dN0-3).

Patients with LABC should be managed by a multidisciplinary team. Treatment typically includes neoadjuvant chemotherapy, surgery, and radiation therapy. The vast majority of patients will have clinical response to therapy. Prior to the use of neoadjuvant chemotherapy, long-term survival was uncommon. Long-term survival has been greatly improved with aggressive trimodality treatment. Only about 10% of patient's have metastatic disease at presentation.

The subset of patients who have isolated ipsilateral supraclavicular lymph nodal metastases at presentation with no other evidence of distant metastases constitutes about 1% of patients who present with carcinoma breast.[5] These patients who were previously classified under stage IV, are now

classified in stage IIIC, since their survival is almost equivalent to that of stage IIIB. Patients in this subset should not be under treated and there is still a possibility of cure.[6] There are no standard guidelines of treatment for this group of patients.

There is very little evidence regarding the management of these patients, especially in Indian literature. Hence we decided to study patients who were treated at our institute, with ipsilateral supraclavicular nodal metastases at diagnosis and with no other evidence of distant metastases.

MATERIALS AND METHODS

A retrospective study of patients who presented with carcinoma breast, treated at Cancer Institute (WIA) from the year 2000 to 2008 was done. The total number of patients who were diagnosed to have invasive cancer of the breast, during the study period was 5587. Of the 5587 patients, we identified 60 patients who presented with ipsilateral supraclavicular lymph nodal metastases but no evidence of other distant metastases.

Patients with distant metastases other than ipsilateral supraclavicular metastases were excluded. Patients with bilateral breast cancers were also excluded. All patients underwent biopsies of the breast tumor, to document invasive carcinoma. Pretreatment evaluation consisted of a thorough history, clinical examination, contralateral mammogram, staging workup that included a chest x-ray, nuclear bone scan, ultrasound of the abdomen and pelvis. All 60 patients had metastatic supraclavicular node, diagnosed either by a fine needle aspiration cytology or an excision biopsy of the lymph node.

Each patient was evaluated in a multidisciplinary planning clinic before therapy was initiated. The clinical team included a surgical oncologist, a medical oncologist, along with a radiation oncologist and was supported by a breast radiologist.

After obtaining an informed consent, treatment was initiated. Most patients were treated with concurrent chemotherapy and radiotherapy. On day 1 of treatment, patients received the specified regimen of chemotherapy followed by initiation of radiation to the breast, axilla and supraclavicular region from day 2. Radiotherapy consisted of external beam radiotherapy to the involved breast, axilla and the supraclavicular region to a total dose of 40 Gy in 4 weeks, usually in fractions of 2 Gy daily and 5 fractions per week. The fields used were medial and lateral tangential fields with acceptable dose to the lungs and heart.

The chemotherapeutic regimens were FAC, FEC, CMF and TE.

DRUG	DOSE
Adriamycin	40 mg/m^2
Methotrexate	60 mg/m^2
5 Fluoro-uracil	600 mg/m^2
Cyclophosphamide	600 mg/m^2
Paclitaxel	175 mg/m^2

Response of the primary and regional nodes were noted at the completion of chemoradiotherapy. Anti-estrogens were started according to their estrogen and progesterone receptor status. These patients were followed up in a 3 monthly interval with clinical examination. All patients underwent metastatic workup annually. Some patients underwent surgery.

Patient's who relapsed were identified and appropriate treatment was given. Recurrence patterns on follow up were also noted. Follow up of these patients was updated till March 2011 or till their death. Patients who had defaulted during treatment or refused further treatment were also noted.

Statistical analysis was done using Pearson's chi-square test for univariate analysis and multinominal logistic regression analysis for multivariate analysis. Survival was calculated using life-tables analysis and various factors influencing survival were compared using Cox Regression analysis. All statistical analysis was done using SPSS for Windows version 14.

REVIEW OF LITERATURE

Breast cancer is the most common cancer among women in India.[7] The incidence of breast cancer too has shown a steady increase in the past few decades. The current Crude incidence rate (CIR) of breast cancer in the MMTR (Madras Metropolitan Tumor Registry) is 30.2.

The crude incidence rates of breast cancer has steadily risen from 14.3 in the year 1982, which is the year of starting the Madras Metropolitan Tumor Registry (MMTR) at the Cancer Institute, to 30.2 in the year 2008. It is seen that the incidence amongst the urban Indian women is higher than in the rural population. Among the metropolitan cities, the incidence is highest in Chennai followed Mumbai, Delhi and Bangalore. In our country we are seeing a rise in the incidence of disease in the younger age groups i.e, less than 40 years. In the US and UK the percentage of breast cancers in women less than 40 years is around 6% whereas in our country it is as high as 23%.

Conversely the proportion of older women with the disease is 45% in the affluent countries while it is only 20%.[8]

The receptor status – Estrogen(ER) and Progesterone(PR), is one of the most important predictive factors in breast cancer. use of hormonal agents like Tamoxifen, Aromatase inhibitors and a host of other drugs is determined by the expression of the hormonal receptors by the breast tumors. There was an excess of receptor negative women in our population both in the premenopausal and the postmenopausal woman.

In the MMTR data, there was a steady increase in the Crude incidence rates with rising educational levels. The CIR was 8 in illiterate women, compared to 40 among literate women. The incidence of the disease was highest among high income groups as compared to low and middle income groups.
In our own city as per the MMTR statistics available, stages II and III cancers account for 55% with a mere 1% in stage I cancer. This is in contradiction to the western population where the incidence of stage I cancer accounted for 60%.[9]

EVOLUTION OF TREATMENT

The study of history of treatment of breast cancer dates back to the era of Galen (130 – 200 AD), when it was believed that cancer is a result of "black bile" and the treatment therefore was to let out the bile. In the end of 19th century after the advent of anaesthesia and antisepsis, surgery became the main stay of treatment.

The treatment evolved as the understanding of the disease biology improved. According to the Halsteadian concept, put forth by Sir William Halstead in 1890, breast cancer is a localized disease in the initial stages and there is a predictable , orderly spread of the disease from the breast to the regional nodes and then to the systemic circulation.[10] Hence treatment in the Halsteadian era was Radical en bloc mastectomy and it was believed that more radical the surgery, better the survival. This formed the basis for the era of Radical, Ultra Radical and Extended mastectomy.

In 1980, Bernard Fischer put forth his theory that breast cancer is a systemic disease right from it's inception. The treatment needs to be therefore directed to systemic therapy.[11]

In 1994, Samuel Hellman put forth his theory of " Spectrum Hypothesis". This stated that breast cancer was a spectrum of diseases with one end of the spectrum being localized and on the other end was a systemic disease. Today we accept the spectrum theory and the treatment is thus aimed at the local and the systemic components according to the stage of the disease.[12]

LYMPHATICS

The subepithelial and the subdermal lymphatic plexus are confluent with the subareolar plexus, which in turn communicate with the fine lymphatics of the lactiferous ducts. Lymph flows unidirectionally in valvular lymphatics from the superficial to the deep and toward the regional lymph nodes. The lymph from the breast primarily drains into the axillary lymph nodes. They are divided into the central, apical, medial, lateral, anterior and posterior groups. Surgeons and pathologists group the axillary lymph nodes according to their relationship to the pectoralis minor muscle. Level I consists of nodes lateral to the pectoralis minor. Level II consists of nodes deep to the muscle and level III consists of nodes medial to this muscle. The internal mammary nodes are found in the second to sixth intercostal spaces at the sternal border.

As a consequence of obstruction to lymph flow by the neoplastic process, reversal of lymph flow is evident. Central and medial lymphatic of the breast pass medially, perforate the pectoralis major muscle and thereafter terminate in the internal mammary nodal chain. The right internal mammary nodal group enters the right lymphatic duct and the left enters the main thoracic duct. The presence of supraclavicular lymph nodes results from lymphatic permeation and subsequent obstruction of the deep cervical nodes of the jugular subclavian confluence.[13]

Gross communications from the interstices of the connecting lymphatics from each breast provides ready access to the lymphatic flow to the contralateral axilla and the breast. This explains the occasional metastatic involvement of opposite axillary nodes.

According to the AJCC Staging System for Breast Cancer, nodal metastases located in the supraclavicular fossa are staged as loco-regional metastases (N3c). Lymph node metastases situated above the supraclavicular region are not mentioned, but should be considered as distant metastases.[14]

PROGNOSTIC FACTORS

A prognostic factor is one which at the time of diagnosis or surgery is associated with outcome – overall survival, disease free survival. The prognostic factors include axillary nodal status, tumor size, grade, age, menopausal status, receptor status, presence of lymphovascular invasion, cerbB2. The axillary lymph nodal status is still the most important factor that affects the prognosis. The probability of recurrence is higher for women with histologically positive axillary lymph nodes and increases with each additional lymph node. Axillary lymph node dissection provides prognostic information, but has minimal therapeutic benefit or none, especially in women with clinically negative axillary lymph nodes and is responsible for the morbidity associated with breast surgery.

PREDICTIVE FACTORS

A predictive factor is one that helps make treatment decisions, particularly with regards to a choice of drug or modality of treatment. The most important predictive factor is the receptor status – ER/PR and the cerbB2 status.

.

AJCC TNM STAGING 2009

PRIMARY TUMOR (T)

TX : Primary tumor cannot be assessed

T0 : No evidence of primary tumor

Tis : Intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated invasion of normal breast tissue

Tis (DCIS): Ductal carcinoma in situ

Tis (LCIS): Lobular carcinoma in situ

Tis (Paget's): Paget's disease of the nipple with no tumor.

T1: Tumor not larger than 2.0 cm in greatest dimension

- T1mic: Microinvasion not larger than 0.1 cm in greatest dimension
- T1a: Tumor larger than 0.1 cm but not larger than 0.5 cm in greatest dimension
- T1b: Tumor larger than 0.5 cm but not larger than 1.0 cm in greatest dimension
- T1c: Tumor larger than 1.0 cm but not larger than 2.0 cm in greatest dimension

T2: Tumor larger than 2.0 cm but not larger than 5.0 cm in greatest dimension

T3: Tumor larger than 5.0 cm in greatest dimension

T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below

T4a: Extension to chest wall, not including pectoralis muscle

T4b: Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c: Both T4a and T4b

T4d: Inflammatory carcinoma

REGIONAL LYMPH NODES (N)

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)

N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral axillary lymph node(s)

N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent[a] ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis

N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

N2b: Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis

N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent[a] ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a: Metastasis in ipsilateral infraclavicular lymph node(s)

N3b: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c: Metastasis in ipsilateral supraclavicular lymph node(s)

DISTANT METASTASES (M)

MX: Presence of distant metastases cannot be assessed

M0: No distant metastases

M1: Distant metastases

AJCC STAGE GROUPINGS

Stage 0

Tis, N0, M0

Stage I

T1, N0, M0

Stage IIA

T0, N1, M0

T1, N1, M0

T2, N0, M0

Stage IIB

T2, N1, M0

T3, N0, M0

Stage IIIA

T0, N2, M0

T1, N2, M0

T2, N2, M0

T3, N1, M0

T3, N2, M0

Stage IIIB

T4, N0, M0

T4, N1, M0

T4, N2, M0

Stage IIIC

Any T, N3, M0

Stage IV

Any T, Any N, M1

TREATMENT FOR BREAST CANCER:

Surgery, radiotherapy and chemotherapy form the basic foundation for treating breast cancer patients. But newer modalities like targeted therapy and immunotherapy are joining a growing armamentarium of tools for therapy and support.

Surgery forms the mainstay of treatment for early breast cancer. In stage I and II, surgery forms initial treatment (modified radical mastectomy or breast conservation surgery), followed by adjuvant chemotherapy. In stage III, neoadjuvant therapy is used followed by mastectomy. Metastatic disease is treated with systemic therapy and local therapy being reserved for few situations.

CRITERIA FOR INOPERABILITY (Haagenson)[15]

1. Extensive edema of the skin over the breast is present.
2. Satellite nodules are present in the skin over the breast.
3. Intercostal or parasternal tumor nodules are present.
4. Edema of the arm.
5. Proven supraclavicular metastases are present.
6. Inflammatory carcinoma.
7. Distant metastases are demonstrated.
8. When any two, or more, of the following signs of locally advanced carcinoma are present:
    a. Ulceration of the skin.
    b. Edema of the skin of limited extent (less than one-third of the skin over the breast involved).
    c. Fixation of the tumor to the chest wall.

d. Axillary lymph nodes measuring 2.5 cm, or more, in transverse diameter and proved to contain metastases by biopsy.
e. Fixation of axillary lymph nodes to the skin or the deep structures

ADJUVANT SYSTEMIC THERAPY

The goal of adjuvant systemic therapy is to prevent the recurrence of breast cancer by eradicating micrometastates that are present at the time of diagnosis. In current practice, three systemic treatment modalities are widely used as adjuvant therapy for early stage breast cancer. These modalities are (1) endocrine treatment such as tamoxifen, aromatase inhibitors or ovarian suppression, (2) anti-HER-2 therapy with the humanized monoclonal antibody trastuzumab and (3) chemotherapy. Selection of adjuvant treatment is determined by the biological features of the breast cancer.

Overview of Adjuvant Treatment Approaches in Breast Cancer

Tumor HER Status	***Tumor Hormone-Receptor Status***	
	Positive	***Negative***
HER-2 negative/normal	Endocrine therapy ±chemotherapy	Chemotherapy
HER-2 positive/overexpressed	Endocrine therapy + chemotherapy + trastuzumab	Chemotherapy + trastuzumab

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy consisting of multiple cycles of polychemotherapy, is well established as an important strategy for lowering the risk of breast cancer recurrence and improving survival. Multiple cycles of adjuvant chemotherapy, typically including anthracycline-based regimens, are recommended for the majority of patients with node-positive and higher risk node-negative tumors. Use of taxanes can contribute to significant improvement in outcomes, especially among women with node-positive breast cancer.

ADJUVANT HORMONAL THERAPY

Tamoxifen is the agent most widely studied as adjuvant endocrine therapy for breast cancer. Tamoxifen administered for a duration of 5 years results in a 41% reduction in the annual rate of breast cancer recurrence and a 34% reduction in the annual death rate for women with ER-positive breast cancer.[16] The optimal duration of tamoxifen therapy appears to be 5 years; extending tamoxifen therapy beyond 5 years in patients with no evidence of tumor recurrence has not led to further improvements in disease-free or overall survival.[17] In the past 5 years, multiple clinical trials have examined the role of aromatase inhibitors (AIs) as adjuvant endocrine therapy for early breast cancer. Tamoxifen acts by blocking estrogen stimulation of breast cancer cells, inhibiting both translocation and nuclear binding of the ER. This alters transcriptional and posttranscriptional events mediated by this receptor. Tamoxifen has agonistic, partial agonistic, or antagonistic effects, depending on the species, target, or end points that have been assessed. Although tamoxifen works by binding to the estrogen receptor, AIs function through inhibition of the aromatase enzyme that converts androgens into estrogens. The result is profound estrogen depletion in postmenopausal women. There is convincing data from a large randomized trial ATAC, that

aromatase inhibitors are fast replacing the anti-estrogens as the first line of management.[19] In premenopausal women, ovarian ablation is achieved by surgical removal or with radiocastration or by Gonadotropin releasing hormone (GnRH) agonists.

RADIOTHERAPY

The role of radiotherapy in the adjuvant setting post mastectomy RT, is to reduce the locoregional recurrence. RT has also been used along with chemotherapy in the neoadjuvant setting. RT is a part of treatment in breast conservation therapy. Radiotherapy has been used at Cancer Institute for LABC prior to the availability of chemotherapy.[20]

SUPRACLAVICULAR NODAL METASTASES

At the turn of the twentieth century, Halstead, who devised the first truly radical mastectomy, had extended his operation to include dissection of the supra-clavicular region. He had performed supraclavicular dissection in 119 cases. None of those patients survived at 5 years.[10]

Jackson et al, in 1966 did a retrospective analysis on the significance of supraclavicular lymph node metastases. One hundred and seventy four patients developed supraclavicular

lymph node metastases after radical mastectomy amongst 1,461 early breast cancer patients. Eighty one of these patients developed these nodes as the first clinical evidence of recurrence. Evidence is presented from the literature and from this study that most of these metastases were present at the time of the mastectomy. It is suggested that, although they may be the only obvious metastases, supraclavicular nodes are usually evidence of widely spread disease. Of these 81 patients, 5% survived 10 years from the radical mastectomy. The findings of this study implied that 'radical' treatment did not alter their ultimate survival, but it did give greater palliation than simpler treatment.[21]

Clinically, ipsilateral supraclavicular lymph node metastases (ISLM) in breast cancer can be classified into 2 manifestations: metachronous and synchronous. Synchronous ISLM (T1-4, N3, M0) is stage IIIc. Metachronous ISLM is isolated supraclavicular lymph node relapse after curative treatment. Although both are featured with ipsilateral supraclavicular lymph node metastases they are two clinical entities needing to be addressed differently.

In 1997, Debois J et al, found that the data on supraclavicular lymph nodes are rather scarce, when compared with the literature on axillary nodes. He reviewed data on the incidence, the risk factors, the possibilities of the different adjuvant therapies in the prevention and the prognosis of a supraclavicular metastatic node in a patient with breast cancer. He concluded that the prognosis is rather dismal as supraclavicular nodes are mostly the prelude to new metastases.[22]

PREDICTIVE FACTORS FOR ISLM:

Shin Cheh Chen et al, analysed the predictive factors of supraclavicular lymph node metastases in breast carcinoma and found that the incidence of supraclavicular lymph node metastases was higher in the groups with >4 positive nodes and in those with axillary level II or III involved nodes. Selective use of comprehensive radiotherapy for these high-risk patients will achieve good loco regional control. In patients with axillary level I involved nodes and ≤4 positive nodes, the incidence was 4.4%. If level III nodes were involved, the rate of supraclavicular lymph node metastases was 15.1%.[23]

PROGNOSTIC FACTORS FOR ISLM:

Kirikuta et al, in his retrospective analysis of ISLM, found that the prognostic significance of supraclavicular lymph node involvement at primary diagnosis or as a relapse is similar, both have the same significance as the first distant relapse and are characterized by a poor prognosis. The axillary lymph node metastasis status and chemotherapy after occurrence of ISLM were independent prognostic predictors for metachronous ISLM, whilst primary tumor size and radiotherapy after diagnosis of ISLM ($P = 0.022$) were independent prognostic factors for synchronous ISLM .[24]

SCL METASTASES AND TNM STAGING

Patient's with breast cancer who present with supraclavicular metastases have a poor prognosis. The presence of supraclavicular metastases was one of the original signs of inoperability identified by Haagensen and Stout. In 1987, the International Union against Cancer/American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system changed the classification of patients with supraclavicular metastases from N3 to M1 to reflect the poor prognosis of patients with this presentation.[25] In 2001, Brito et al reported on a pooled analysis of three M.D. Anderson

Hospital protocols and found that patients with regional stage IV disease had better outcomes than patients with visceral stage IV disease. Clinical course and prognosis of patients with isolated supraclavicular metastases at presentation were similar to those of patients with stage III B locally advanced breast cancer.[6] Thus, classifying supraclavicular node as a distant metastases may lead to undertreatment of patients. Hence in 2003, the AJCC has further amended the staging classification to include patients with supraclavicular metastases at diagnosis in the IIIC category.[14]

COMBINED MODALITY THERAPY FOR ISLM:

Eugene H. Huang did a retrospective analysis of 71 patients with ISLM at presentation. Radiotherapy achieved excellent locoregional control after surgery for patients with ISLM, who achieved a complete response of the supraclavicular disease after neoadjuvant chemotherapy. For patients who achieved a complete response of the supraclavicular disease by physical examination, ultrasonography of the SCV fossa may help assess the risk of disease recurrence.[26]

Most of the patients who present with LABC and ISLM have very poor survival with standard treatment modalities, and

over the past 20 years combined modality therapy has been used to improve local and systemic control. Uncontrolled trials strongly suggest that patients with any stage of locally advanced breast cancer achieve high response rates after induction chemotherapy. Most of these patients can be rendered disease free after combined modality therapy, and their disease-free and overall survival rates appear to be improved when compared with historical controls.

Pergolizzi et al, conducted a prospective nonrandomized trial in order to evaluate the role of radiotherapy (RT) with "radical dose" to the supraclavicular fossa. He compared systemic therapy alone (arm A) to integrated and aggressive treatment - systemic therapy plus radiotherapy (arm B). In comparison to arm A, patients in arm B had longer median time to progression of 20 months and better median overall survival of 41 months. These data demonstrated that a better event free survival could be achieved in patients with ISLM submitted to induction CT and radical irradiation. This also translated into a longer survival although this did not achieve statistical significance. He also stressed the importance of local control by RT.[27]

Lena Mario et al, assessed the efficacy of two combined modality approaches (chemotherapy plus radiotherapy Vs chemotherapy plus mastectomy) in a total of 132 women with locally advanced breast cancer. There was no significant difference between the two treatment groups in terms of patterns of treatment failure, median duration of response, and total survival. Treatment was not influenced by menopausal or estrogen receptor status. The results of the study failed to indicate that surgery per se improved the overall results, including local control, over radiotherapy in a combined modality setting.[28]

Gardin et al analysed the prognostic factors in patients homogenously treated with combined modality approach (chemotherapy, RT and surgery)**.** Univariate analysis showed that age, receptor status and clinical and pathological response to primary chemotherapy did not appear to influence treatment outcome significantly, whereas stage, presence of inflammatory disease and number of involved nodes had a significant impact on both overall survival and progression free survival.[29]

Sanchez ER et al assessed the factors affecting the outcome of patients presenting with LABC with combined

modality approach of treatment. In univariate analysis, clinical stage, pathological stage, oestrogen receptor status and type of therapy were significant predictors for disease-free survival (DFS) and overall survival (OS). However, in a multivariate analysis, only clinical stage was a significant predictor for both DFS and OS, while ER status was a significant predictor for OS.[30]

In patients presenting with ISLM as the only site of metastases at diagnosis, who receive treatment with combined modality approach, it was found that, nearly two-thirds of the patients developed a recurrence by 5 years. Loco-regional recurrence was the site of first recurrence in one-third of the patients by 5 years.[30]

Survival benefit of neck dissection for patients with breast cancer with supraclavicular lymph node metastasis was assessed in a study by Shin Chen et al from Taiwan. Neck dissection was defined as curative intent to remove all nodes and soft tissue in neck level IV and part of III and V. Forty-nine in 127 SLNM patients had received neck dissection. The 5, 10 years OS for those who received neck dissection or not were 30.6%, 16.1%, and 14.9%, 4.7% respectively which was

statistically significant. In multivariate analysis, neck dissection, disease-free interval and hormonal therapy were independent prognostic factor for survival.[31]

Shin-Cheh Chen et al, performed a study to analyze the survival of breast cancer patients with isolated supraclavicular lymph node metastasis and assess whether ISLM is distant metastasis or not. The survival after ISLM was compared with that of patients who developed local recurrences and who had distant metastasis. The 5-year overall survival (OS) rates after ISLM, local relapse, and distant metastasis were 33.6%, 34.9%, and 9.1% respectively. Good neck control either by surgery or chemotherapy achieved better survival.[23]

There still is debate as to whether breast carcinoma patients with isolated supraclavicular recurrence should be considered to be patients with disseminated disease or patients for whom aggressive treatment with curative intent is justified.
Maurice et al, followed up of 42 patients with isolated supraclavicular recurrence, without other sites of distant disease. Although complete remission can be obtained in most patients with isolated supraclavicular recurrence, the prognosis for these patients is poor. The distant disease–free survival rate

was better for the 25 patients who underwent radiotherapy as part of the treatment for supraclavicular recurrence than it was for the 17 patients who did not receive radiotherapy (*P* _ 0.06); Patients who had received axillary and supraclavicular radiotherapy as part of treatment had better distant disease free survival. Involved field radiotherapy appears to play an important role in the treatment of supraclavicular recurrence and may improve the distant recurrence–free survival.[32]

Ivo A. Olivotto conducted a retrospective analysis and compared long-term survival in a population-based cohort of patients with isolated supraclavicular metastases (nodal-M1) to outcomes of patients with stage IIIB or M1 (other) disease at presentation**.** A total of 51 (1%) had supraclavicular but no other metastases. The median overall survival durations were 2.4 years for supraclavicular cases. A small proportion of M1 (other) patients (2%), 9% of IIIB patients, and 13% of the patients presenting with supraclavicular lymph node metastases alone survived longer than 20 years from diagnosis.

A limitation of the study is that the majority of patients with supraclavicular metastases had the diagnosis made clinically. The 5 year OS for stage IIIB, stage IIIC, stage IV

was 43%, 33% and 15% respectively. Breast cancer–specific survival at 20 years was 24.1% for nodal-M1 cases, 30.2% for IIIB cases and 3.9% for M1 (other) cases (P <.0005). Patients with supraclavicular metastases at diagnosis have significantly better outcomes than patients with M1 (other) disease and overall survival similar to patients with IIIB disease.[5]

Brito et al, in 2001 reviewed the records of all 598 patients with LABC who were treated on three prospective trials of combined-modality therapy for LABC at M.D. Anderson Cancer Center between 1974 and 1991. He identified 70 patients who presented with ipsilateral supraclavicular metastases but no evidence of other distant metastases. The median patient age was 49 years (range, 24 to 78 years). The overall response rate (complete response plus partial response) to neoadjuvant chemotherapy was 89%. With a median follow-up duration of 11.6 years (range, 4.8 to 22.6 years), the local-regional control rate was 81%. The median duration of survival was 3.5 years. The median duration of disease-free survival was 1.9 years. The probabilities of survival to 5 and 10 years were 41% and 31%, respectively. The 5 and 10year disease-free survival rates were 34% and 32% respectively. More importantly, with a median follow-up of 11.6 years and a

maximum follow-up of 22.6 years, results indicated that approximately 32% of these patients will remain alive and disease-free at 10 years. The overall survival curve was significantly better than that of patients with metastatic breast cancer. Patients with ipsilateral supraclavicular metastases but no other evidence of distant metastases warrant therapy administered with curative intent, i.e, combined-modality therapy consisting of chemotherapy, surgery and radiotherapy.[6]

Alexandros Adravanis et al, analysed the results of multidisciplinary therapy of Locally far-advanced with fixed perioperative sequence of epirubicin, vinorelbine and fluorouracil chemotherapy, surgery, and radiotherapy. Patients with stage IIIB or IIIC had more pathological responses than Inflammatory breast cancer patients (p = .005). No difference in the probability of recurrence and death was found between stage IIIB/IIIC. Clinically responding patients had longer Recurrence free survival and OS (p = .001 and p = .004), respectively.[33]

PET scan is a functional imaging that has gained widespread acceptance in diagnosis, staging and management of variety of malignancies including breast cancer. The level of

uptake is semiquantified and reported as Standardised Uptake Value (SUV). It is ideal to use PET scan for initial staging (axillary, internal mammary, supraclavicular and mediastinal nodes), recurrences in asymptomatic patients and re-staging patients with locoregional recurrences.

Abraham et al, conducted a prospective trial in patients with SCL metastases by treating them with high dose chemotherapy and peripheral stem cell transplantation. He concluded that the long term outcome was better in patients receiving high dose chemotherapy; whether this result is superior to that achieved with standard therapy alone remains to be confirmed in randomized trials.[34]

RESULTS

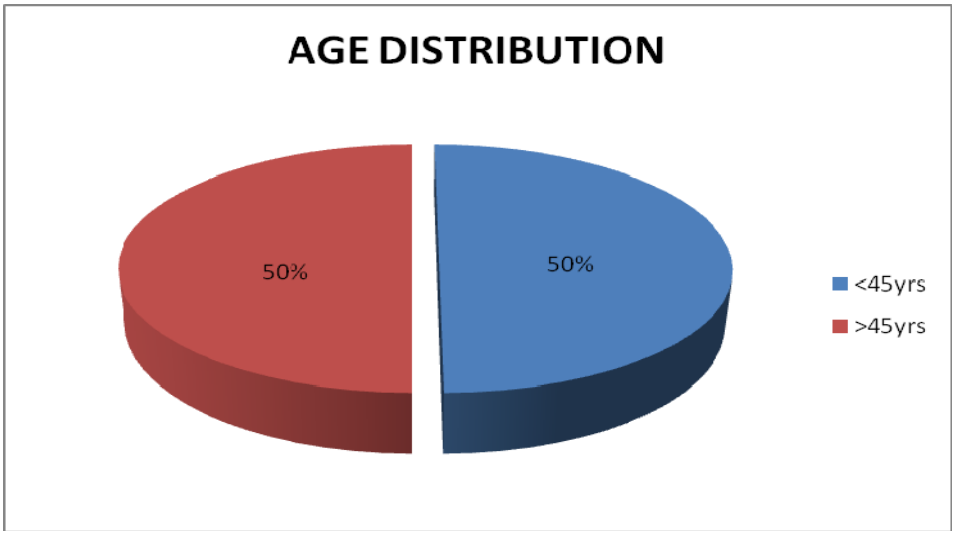
INCIDENCE

In our study, the incidence of isolated supraclavicular nodal metastasis at presentation in patients with carcinoma breast was 1.07%.

PATIENT CHARACTERISTICS:

In our study, the median patient age was 45 years (range 29 – 75 years). (Figure 1)

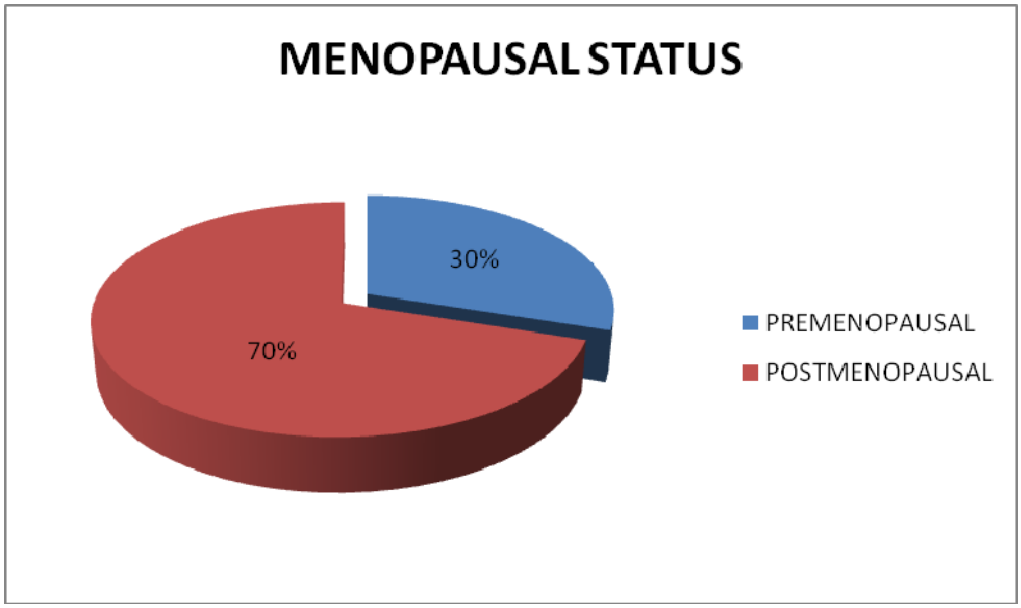
Figure 1



MENOPAUSAL STATUS

18 patients (30%) were premenopausal and 42 patients (70%) were postmenopausal. (Figure 2)

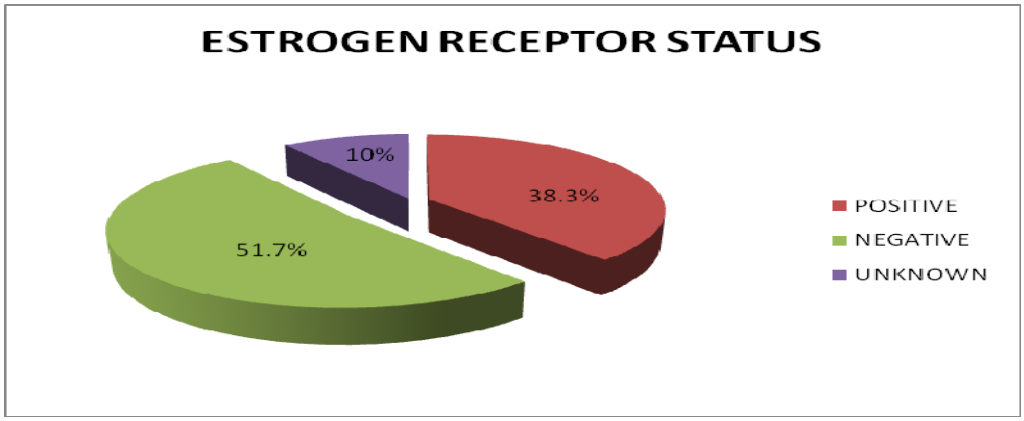
Figure 2



RECEPTOR STATUS

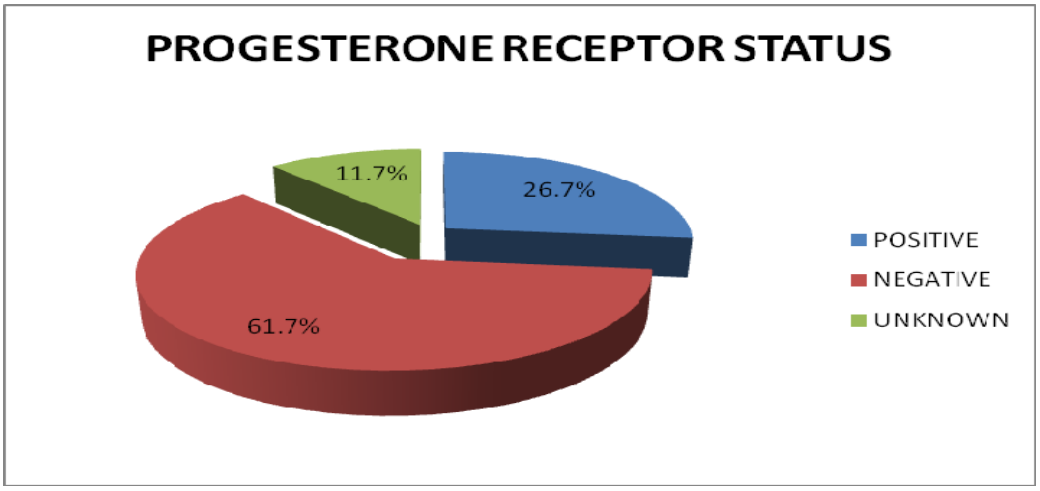
Out of the total 60 patients, estrogen receptor status was available in 54 patients and unknown in 6 patients. (Figure 3)

Figure 3



Out of the total 60 patients, progesterone receptor status was available in 53 patients and unknown in 7 patients. (Figure 4)

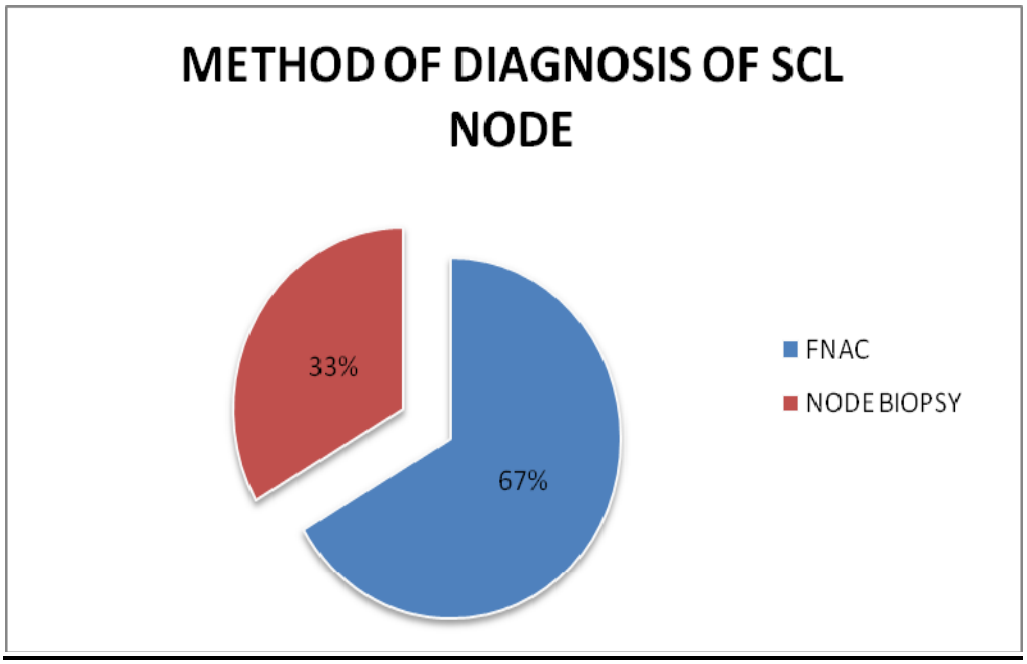
Figure 4



METHOD OF DIAGNOSIS OF SCL NODE:

In our study, 40 patients underwent FNAC of the supraclavicular node and 20 patients underwent node biopsy. (Figure 5)

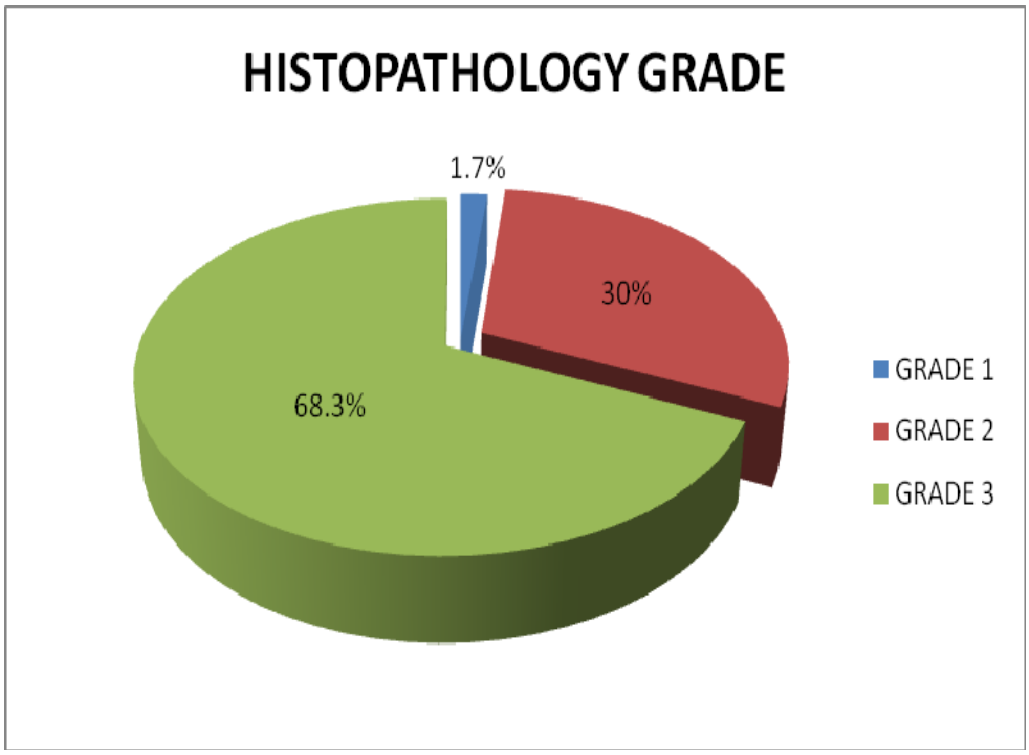
Figure 5



HISTOPATHOLOGICAL GRADE

Out of the total 60 patients, 41 patients (68.3%) had Grade 3 tumor, 18 patients (30%) had grade 2 tumor. (Figure 6)

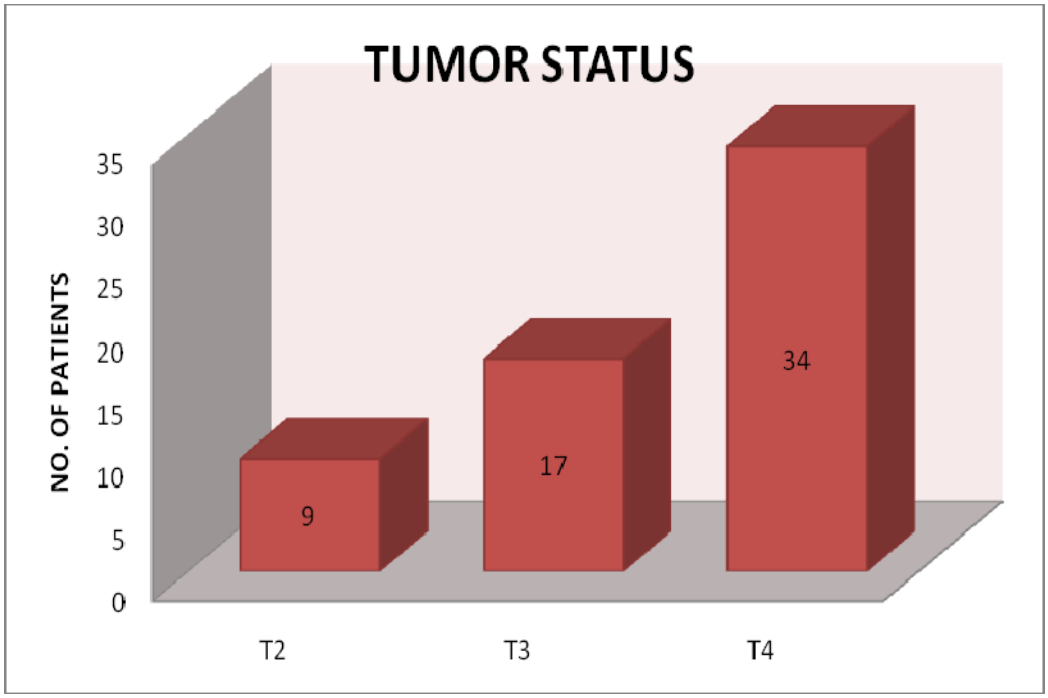
Figure 6



TUMOR STATUS

34 patients (56.7%) belonged to T4 tumor status, 17 patients (28.3%) belonged to T3 and 9 patients (15%) belonged to T2 tumor status. (Figure 6)

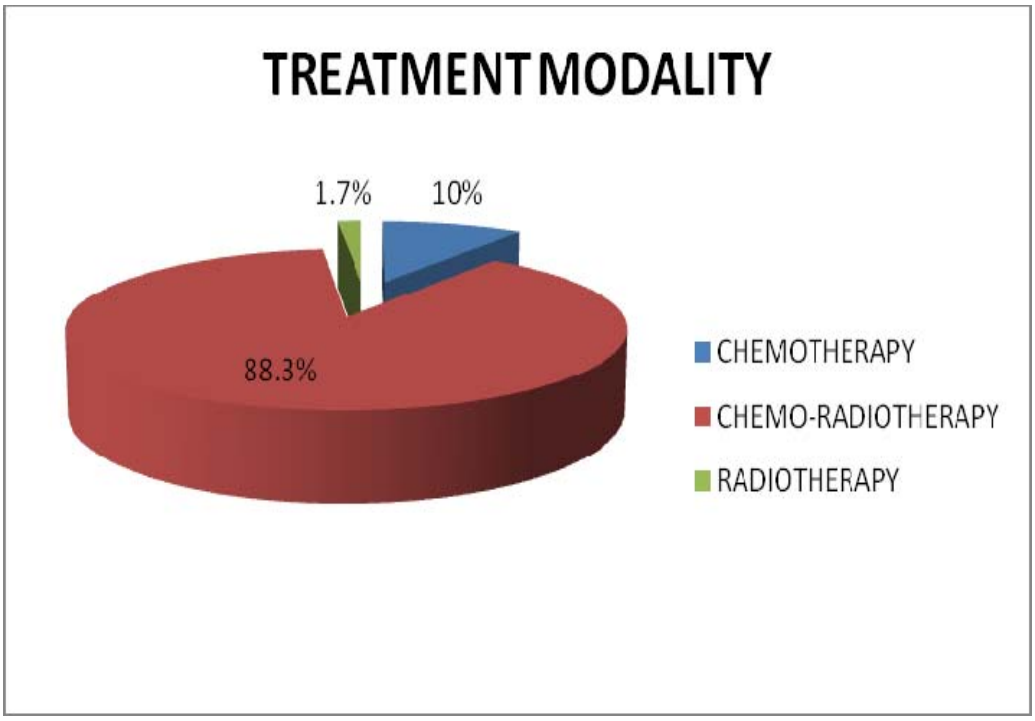
Figure 7



TREATMENT MODALITY

Majority of the patients (88.3%) received concurrent chemo radiotherapy. One patient received radiotherapy alone. Six patients (10%) received chemotherapy alone. (Figure 8)

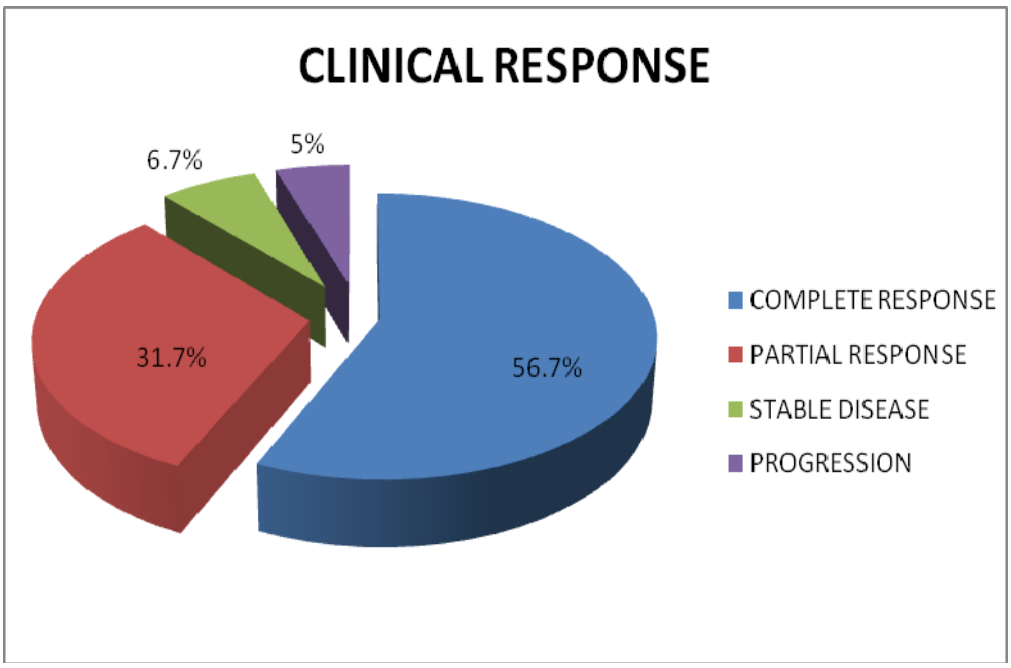
Figure 8



CLINICAL RESPONSE TO TREATMENT

The overall response rate (complete plus partial response) to chemoradiotherapy was 88%. In our study, 57% of patients experienced clinical complete response, 31.7% had a partial response, 6.7% had stable disease. 5% of the patients had disease progression during treatment. (Figure 9)

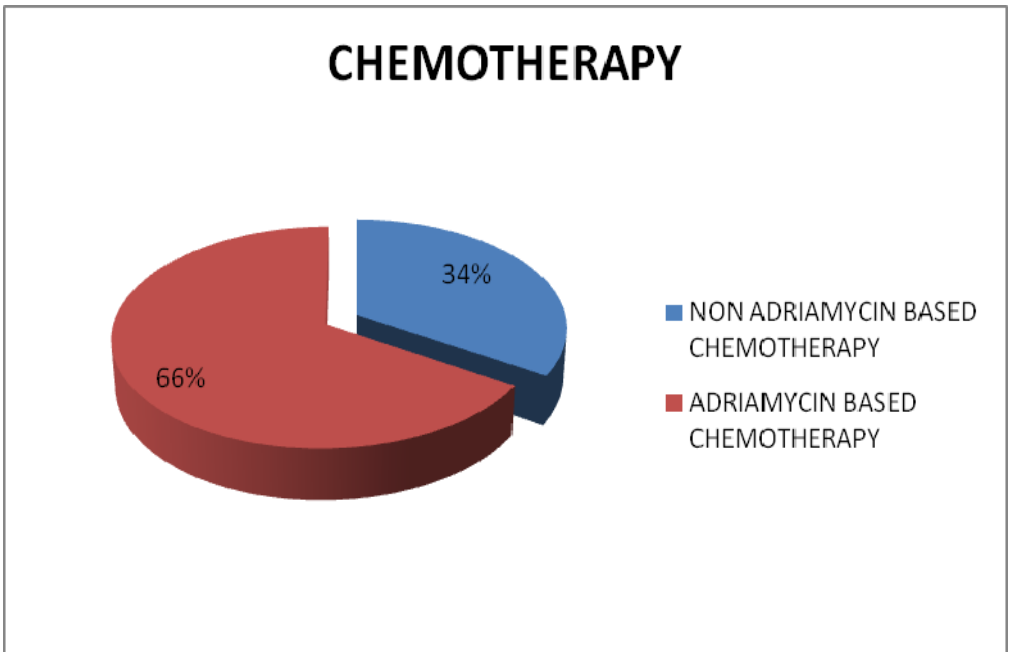
Figure 9



The following chemotherapy regimens were used. (Figure 10)

Endoxan	2	3.4%
CMF	17	28.3%
FAC	33	55.9%
FEC	3	5.1%
TE	3	5.1%
VP16	1	1.7%

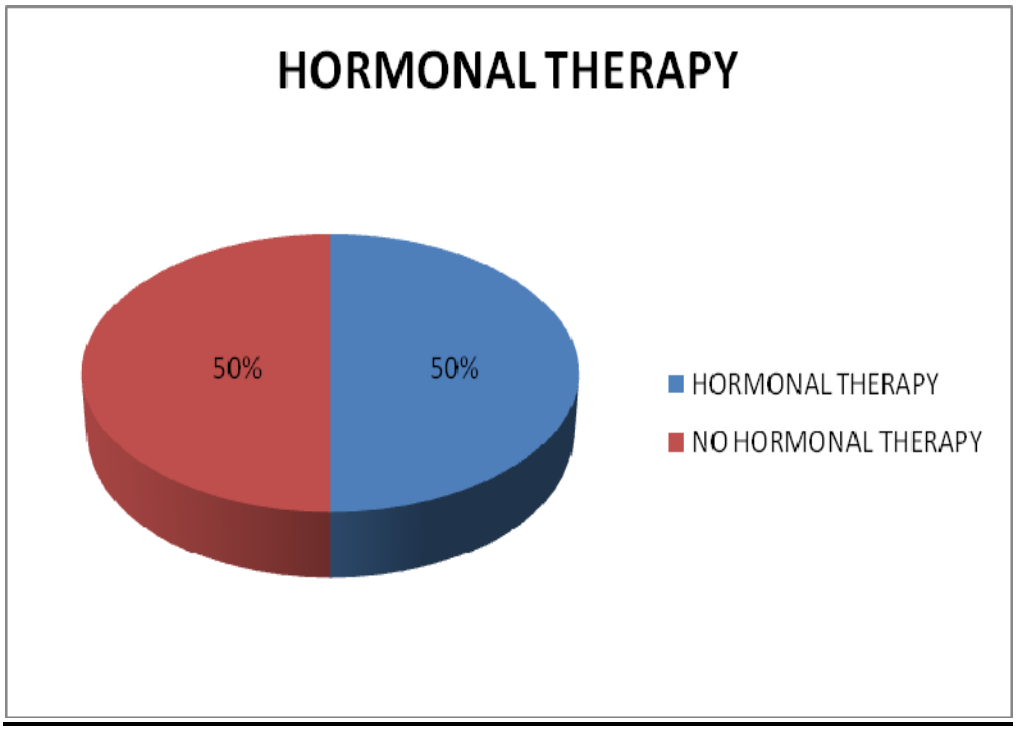
Figure 10



HORMONAL THERAPY

Fifty percent of the patients received Hormonal therapy either in the form of Tamoxifen or Letrozole. Six patients (10%) had bilateral salpingo-oopherectomy. (Figure 11)

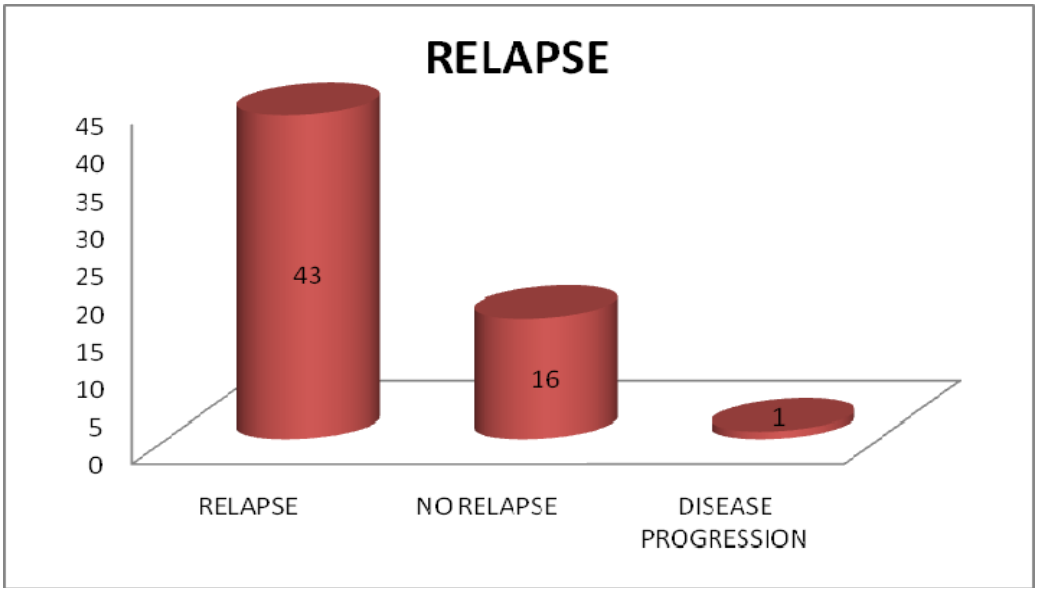
Figure 11



RELAPSE RATES

In our study, 43 patients (71.7%) had relapse of tumor, one patient had disease progression during treatment and 16 patients (26.7%) were disease free till the last date of follow up. (Figure 12)

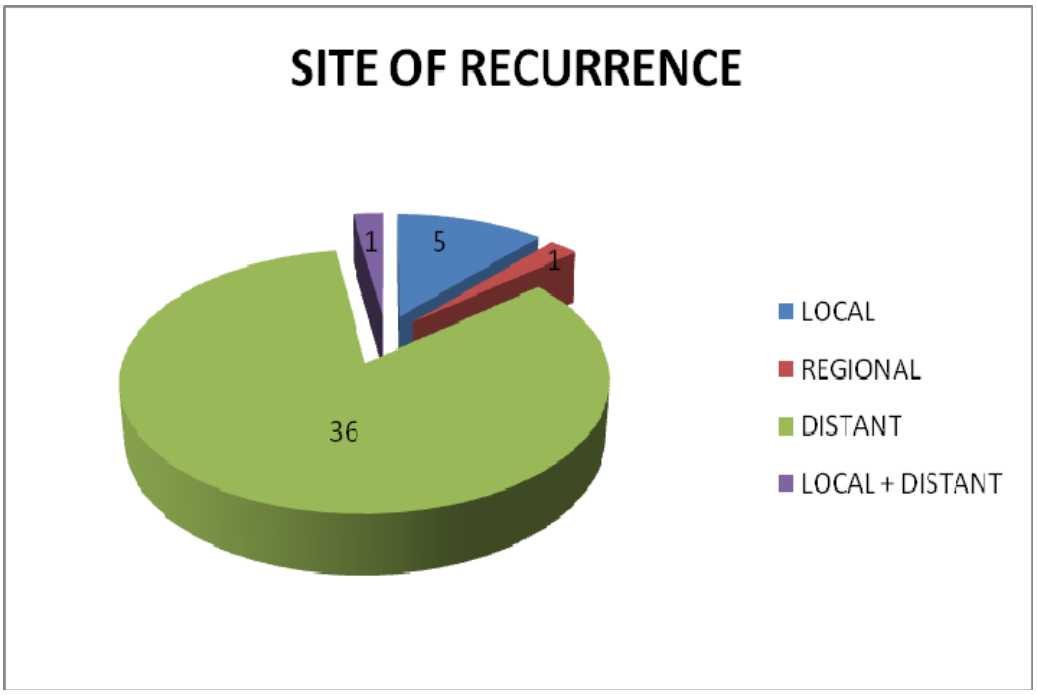
Figure 12



RECURRENCE PATTERNS

The site of recurrence among the 43 patients who relapsed were as follows: Local – 5 (8.3%), Regional – 1 (1.7%), Distant – 36 (60%), Local + distant – 1 (1.7%). (Figure 13)

Figure 13



STATISTICAL ANALYSIS

UNIVARIATE ANALYSIS

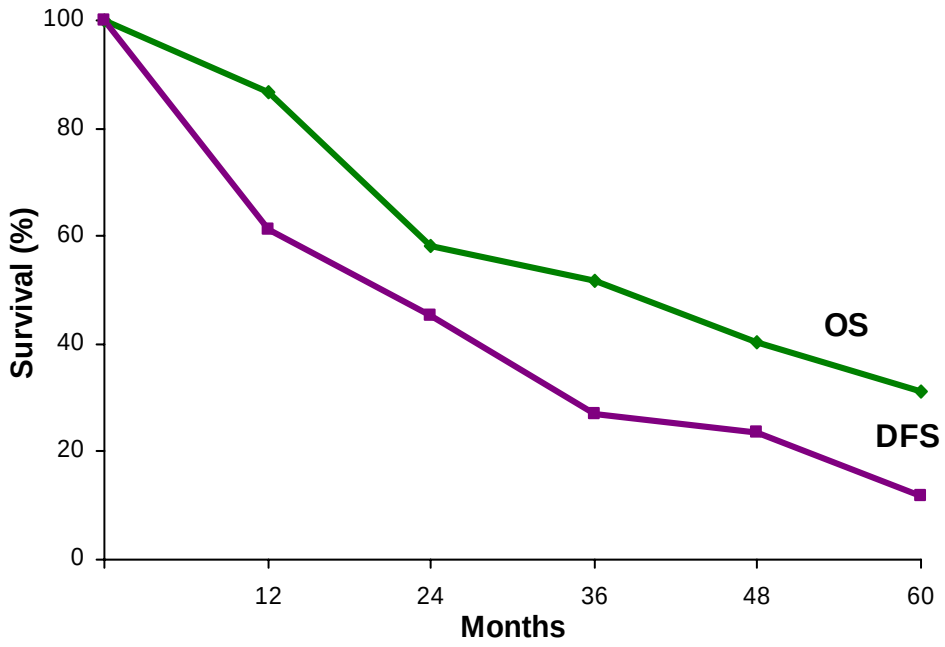
VARIABLE	P VALUE
Age	0.52
Menopausal status	0.81
T stage	**0.04**
ER status	**0.003**
Treatment modality	**0.03**
Clinical response	**0.001**
Hormonal therapy	**0.001**
Histopathological grade	0.61
Adriamycin based chemotherapy	0.32

MULTIVARIATE ANALYSIS

VARIABLE	HAZARD RATIO	CONFIDENCE INTERVAL	SIGNIFICANCE P VALUE
T stage	8.27	1.01 – 67.43	**0.05**
Menopausal status	8.00	1.35 – 47.29	0.08
Estrogen receptor status	4.7	0.73 – 30.37	0.10
Histopathological grade	0.45	0.64 – 14.7	0.80
Treatment modality	0.36	0.10 – 1.29	0.12
Clinical response	3.73	1.26 – 11.05	**0.018**

SURVIVAL CURVE

OVERALL SURVIVAL & DISEASE FREE SURVIVAL



The five year overall survival and disease free survival were 31.3% and 11.7% respectively.

DISCUSSION

Breast cancer is today the most common cancer amongst the women of developed countries. Of late, the incidence of breast cancer has increased in our country too and it has become the most common cancer amongst women of the four metropolitan cities of our country. Most patients present with locally advanced breast cancer and as metastatic breast cancer. Advances in investigative modalities and newer treatment options combined with screening have decreased the mortality due to the disease. The current treatment regimens have improved the survival of LABC.

Isolated ipsilateral supraclavicular lymph nodal metastases at presentation is a rare but important occurrence in breast cancer. The presence of supraclavicular nodal metastases was earlier considered as a predecessor to distant metastases. Haagenson et al, achieved no 5-year clinical cures among patients with supraclavicular involvement.[15]

In our study, the incidence of ipsilateral supraclavicular nodal metastases at presentation was 1.07%. Fifty percent of the patients in our study group were above 45 years. Most of them presented with locally advanced primary. About 56.7% of patients had T4 disease at presentation.

Most of the patients (88%) in our study received concurrent chemoradiotherapy. At the Cancer Institute (WIA) Chennai, concurrent chemoradiotherapy began way back in the 1970's, when radiotherapy was given to the large tumors to increase the chance of surgery. With the advent of chemotherapy, the Institute started using both chemotherapy and radiotherapy in a concurrent manner in LABC.

The objective in combining radiotherapy and chemotherapy in LABC was the early introduction of chemotherapy. The two modalities could be synergistic in reducing the tumor and nodal volume, in addition to the chemotherapeutic impact on micrometastases.

The results of our protocol concurrent chemoradiotherapy in the setting of LABC have demonstrated a significant increase in tumor sterility (complete pathological response) and nodal

down staging. This concept has also been applied in patients presenting with ipsilateral supraclavicular metastases.[36]

The intent of treatment for patients with ipsilateral supraclavicular nodal metastases at presentation is curative. Patients who completed the concurrent chemoradiation were assessed for the response to treatment at the end of therapy.

The overall response rate (complete plus partial response) to chemoradiotherapy was 88%, which is comparable with one of the largest series published by Brito et al in 2001,[6] in which he quoted a overall response rate of 89%. In our study, 57% of patients experienced clinical complete response, 31.7% had a partial response, 6.7% had stable disease. 5% of the patients had disease progression during treatment.

The most common chemotherapeutic regimen used was FAC (56%). Sixty-six percent of the patients received adriamycin based chemotherapy.

The factors that we thought, which could affect the response to treatment were age, T stage, grade, ER/PR status and combined modality of therapy (chemoradiation). But on

analyzing our results we found that the only factor which had a bearing upon the response to treatment was the combined modality of therapy ($p = <0.05$).

Surgery was performed only in nine patients (15%). The median interval between the completion of chemoradiation and surgery was 6 months. Out of the 9 patients who underwent surgery, 7 had modified radical mastectomy, 2 patients underwent total mastectomy since axillary dissection could not be performed due to the nodes being stuck to the axillary vein. Out of the nine patients who underwent surgery only two had complete pathological response.

Since 2005, at our institute, we have been recommending the option of surgery after the completion of concurrent chemoradiation. Patients who completed chemoradiation were observed for a period of 6 months and a metastatic workup was done at the end of 6 months. If the patient showed no evidence of distant metastases, these patients were offered surgery. The rationale being, patients with isolated supraclavicular metastases most commonly relapse with distant metastases. In our study, the low percentage (15%) of patients who underwent surgery, can be explained by the fact that many patients refused surgery after completion of chemoradiation.

In our study, univariate analysis showed that performing surgery was not a significant factor which affected overall survival (p value = 0.33). This result should be inferred with caution, since only a small percentage of patients underwent surgery to achieve statistical significance.

Hormonal therapy was given based upon the ER/PR status. Hormonal therapy included tamoxifen in 57 %, Letrozole in 33% and ovarian ablation in 10% of patients.

The median follow up duration of our study was 30 months (range 5 – 77 months).

On follow up, the median time to relapse was 12 months. Forty-three patients (72%) relapsed during the follow up period. The most common site of relapse was distant metastases constituting about 83%. The most common site of distant metastases being lungs in 44.4%. Out of the 43 patients who relapsed after initial treatment, 19 patients (44%) received treatment for the relapse and the remaining 24 patients (56%) who relapsed were treated with best supportive care. Most of the patients (69%) received chemotherapy at relapse.

Univariate analysis showed that the age, menopausal status, histopathogical grade, surgery and type of chemotherapy did not appear to influence the treatment outcomes significantly, whereas the T stage (p value = 0.04), ER/PR status (p value = 0.003), combined modality of treatment (p value = 0.03), clinical response to treatment (p value = 0.003) and hormonal therapy (p value = 0.001) had an impact on overall survival.

Multivariate analysis showed that only, T stage (p value = 0.04) and clinical response to treatment (p value = 0.02) had a statistically significant impact on the overall survival. The combined modality of treatment, chemoradiotherapy which was significant in univariate analysis, lost it's significance in the multivariate analysis the results of which are similar to that of other studies.

In our study, patients with T4 tumor status had 8 fold increased risk of disease recurrence or death than T2 tumor. Patients who achieved complete clinical response to chemoradiation had a 3 fold decreased risk of disease recurrence or death.

The 5 year overall survival in our study was 31.3%, which is almost similar to that of the study done by Brito et al (41%).[6] In our study, the median overall survival duration was 38 months (range 5 – 77 months). Our study demonstrated that a significant percent of patients (26.7%), may be long term survivors.

In summary, we suggest that infraclavicular and supraclavicular lymph nodes are part of a continuum in the regional lymph node drainage of the breast. Axillary lymph node levels 1, 2, and 3 and the infraclavicular and supraclavicular lymph nodes are not separated on the basis of functional differences. They are separated according to arbitrary anatomic boundaries and gradual worsening of prognosis when treatment consists of chemotherapy alone or radiation therapy alone.

It therefore seems appropriate that, patients with isolated ipsilateral supraclavicular nodal metastases at presentation should be treated with radical intent. Treatment should include concurrent chemoradiotherapy, followed by a definitive treatment to the local area if rendered operable by a modified radical mastectomy.

CONCLUSION

Patients with breast cancer who present with isolated ipsilateral supraclavicular nodal metastases, though previously thought to be a subset of patients with poor prognosis and a predecessor of distant metastases, need definitive treatment with multidisciplinary approach.

In our Institute, we have been practising concurrent chemotherapy and radiotherapy followed by surgery if rendered operable. The 2003 revision of the AJCC breast cancer TNM staging system has appropriately reclassified patients presenting with supraclavicular metastases from M1 to a new category IIIC.

In our study, the incidence of isolated supraclavicular nodal metastases at presentation in patients with carcinoma breast was 1.07%.

In our study, the 5 year overall survival and disease free survival were 31.3% and 11.7% respectively. The overall response rate (complete plus partial response) to

chemoradiotherapy was 88%. About 72% of patients relapsed after the completion of chemoradiotherapy. The median time to relapse was 12 months.

The most common site of relapse was distant metastases constituting about 83%. The most common site of distant metastases was lungs (44%). The median follow up duration was 30 months (range 5 – 77 months).

The T stage and the clinical response to concurrent chemoradiation had a significant impact on the overall survival in multivariate analysis.

Patients with ipsilateral supraclavicular nodal metastases at presentation, but with no other evidence of distant metastases have outcomes more similar to stage IIIB, rather than stage IV. Therapeutic nihilism and sequential palliative interventions alone may well be insufficient unless the patient's performance status indicates that radical treatment will not be tolerated.

The intent of treatment in this subset of patients, therefore should be curative. The definitive multidisciplinary treatment which combines chemotherapy, radiotherapy and surgery has to be the standard of care and will go a long way in improving the treatment outcomes for these patients.

BIBLIOGRAPHY

1. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37(Suppl 8):4.

2. Ries L, Eisner M, Kosary CL, et al. SEER cancer statistics review, 1975 – 2001. Bethesda, MD: National Cancer Institute, 2004.

3. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353(17):1784.

4. Elston CW, Ellis IO. Assessment of histologic grade. In:Elston CW, Ellis IO, eds. The breast. Edinburgh: Churchill Livingstone, 1998:365.

5. Ivo A. Olivotto, Boon Chua, Sharan J. Allan, et al. Long-term survival of patient with supraclavicular metastases at diagnosis of breast cancer. J Clin Oncol 2003;21:851 – 854.

6. Brito RA, Valero V, Buzdar AU, et al: Long-term results of combinedmodality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol 2001;19:628 – 633.

7. Shanta V, Swaminathan R, Nalini S, et al. Population based cancer registry, Cancer Institute (WIA), Chennai. In:Two year report of the population based cancer registries, 1999 – 2000. New Delhi:National Cancer Registry Programme, Indian Council of Medical Research;2005.p.160 – 195.

8. Ries L, Eisner M, Kosary CL, et al. SEER cancer statistics review, 1975-2001; National Cancer Institute, 2004.

9. Desantis C, Howlander N, Cronin KA, et al. Breast Cancer Incidence rates in US women. Cancer Epidemiol Biomarkers, 2011;20(5):733-739.

10. Halstead WS: The results of radical operations for the cure of cancer of the breast. Ann Surg 1907;46:1 – 5.

11. Fischer B. Laboratory and clinical research in breast cancer- a personal adventure.Cancer Research 1980;40(11):3863-3874.

12. Hellman S, Heimann R. The clinical significance of tumor progression: breast cancer as a model. Cancer J 2000;6(2):131-133.

13. Anson NJ,McVay OB,Thoracic walls,Breast or mammary region. In Anson.N.NJ McVay OB ,Surgical Anatomy,Vol I-Philadelphia,NB Saunders,1971,pp 330-369.

14. Singletary SE, Allred C, Ashley P et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20:3628–3636.

15. Haagensen CD, Stout AP: Carcinoma of the breast: Criteria of inoperability. Ann Surg 1943;118:859-870.

16. Early Breast Cancer Trialists Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;365(9472):1687.

17. Bryant J, Fisher B, Dignam J. Duration of adjuvant tamoxifen therapy. J Natl Cancer Inst Monogr 2001;30:56.

18. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med 2003;348(24)2431.

19. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365(9453):60.

20. Shanta V, Krishnamurthi S. Pre-operative multimodal therapy for locally advance non-inflammatory breast cancer. Clin Oncol (R Coll Radiol) 1991;3:137 – 140.

21. Jackson SM: Carcinoma of the breast: The significance of supraclavicular lymph node metastases. Clin Radiol 1966;17:107 – 114.

22. Debois JM. The significance of a supraclavicular node metastasis in patients with breast cancer. A literature review Strahlenther Onkol 1997;173:1 – 12.

23. Chen SC, Chen MF, Hwang TL et al. Prediction of supraclavicular lymph node metastasis in breast carcinoma. Int J Radiat Oncol Biol Phys 2002;52:614–619.

24. Kiricuta IC, Willner J, Kolbl O, Bohndorf W. The prognostic significance of the supraclavicular lymph node metastases in breast cancer patients. Int J Radiat Oncol Biol Phys 1994;28:387–393.

25. Hermanek P, Sobin LH (eds): TNM Classification of Malignant Tumours: International Union Against Cancer (ed 4). New York, NY, Springer, 1987.

26. Huang EH, Strom EA, Valero V et al. Locoregional treatment outcomes for breast cancer patients with ipsilateral supraclavicular metastases at diagnosis. Int J Radiat Oncol Biol Phys 2007;67:490 – 496.

27. Pergolizzi S, Adamo V, Russi E, et al. Prospective multicenter study of combined treatment with chemotherapy and radiotherapy in breast cancer women with the rare clinical scenario of ipsilateral supraclavicular node recurrence without distant metastases. Int J Radiat Oncol Biol Phys 2006;65:25 – 32.

28. De Lena M, Varini M, Zucali R, et al. Multimodal treatment for locally advanced breast cancer. Result of Chemotherapy-radiotherapy versus chemotherapy-surgery. Cancer clinical trials 1981;4: 229 – 236.

29. Gardin G, Rosso R, Campora E, et al. Analysis of prognostic factors in patients homogenously treated with a combined modality approach. Eur J Cancer, 1995;31(9):1428-1433.

30. Sanchez ER, Forgach EP, Mamounas J, et al. Factors affecting outcome in locally advanced breast cancer. Surgical Oncology, 1992;1:347 – 355.

31. Chen SC, Chang HK, Lin YC et al. Prognosis of breast cancer after supraclavicular lymph node metastasis: not a distant metastasis. Ann Surg Oncol 2006;13:1457–1465.

32. Van der Sangen MJ, Coebergh JW et al. Detection, treatment and outcomes of isolated supraclavicular recurrence in 42 patients with invasive breast carcinoma. Cancer 2003; 98(1):11-17.

33. Ardavanis A, Scorilas A, et al. Mutidisciplinary therapy of locally far advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin, vinorelbine, fluorouracil chemotherapy, surgery and radiotherapy.Oncologist 2006;11(6):563-573.

34. Abraham R, Nagy T, Goss PE, Crump M. High dose chemotherapy and autologous blood stem cell support in women with breast carcinoma and isolated supraclavicular lymph node metastases. Cancer 2000;88:790–795.

35. Shanta V, Swaminathan R, Rama R, et al. Retrospective analysis of locally advanced noninflammatory breast cancer from Chennai, South India, 1990 – 1999. Int J Radiat Oncol Biol Phys 2008;70:51 – 58.